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Research Article

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Low Serum Zinc in Critically Ill Patients Fed Oral and Enteral Nutrition in a Brazilian Terciary Hospital: A Cross-Sectional Study

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Abstract

Purpose: *Since zinc is required for immunity and inflammation regulations, this paper aimed to investigate serum zinc levels in critically ill patients receiving Enteral (EN) and Oral Nutrition (ON) and correlate these values with demographic, clinical and laboratory parameters.*

Material and Methods: *This is a cross-sectional study. Researchers collected data from electronic medical records in Intensive Care Units (ICUs) of a Brazilian tertiary hospital. Flame Atomic Absorption Spectrophotometry measured serum zinc (normal range: 70-120 mcg/dl). Evaluated variables: age, sex, diagnoses, ICU type, iron, hemoglobin, leukocytes, C-reactive protein, severity score, and mortality.*

Results: *Researches assessed 203 medical records. Mean zinc score was low (EN: 59.13 ±16.26 mcg/dl; ON: 64.75 ±16.80 mcg/dl; p= 0.010). Mean age was high (EN: 77.48 ± 16.26 years; ON: 75.01 ± 13.03 years; p= 0.012). Iron was positively correlated with zinc in EN (p= 0.012). Age was correlated negatively with zinc in ON (p=0.001). Hemoglobin was correlated positively with zinc in EN (p= 0.007) and ON (p= 0.018).*

Conclusions: *Most of the ICU patients had low zinc. EN had lower zinc levels than ON. Lower hemoglobin, lower zinc in both groups. Lower iron, lower zinc in EN. Old age was correlated with low zinc in ON.*

Keywords: Zinc; Critical Care; Micronutrients; Nutritional Support; Enteral Feeding.

Introduction

Zinc is a ubiquitous micronutrient for microorganisms, plants and animals [1]. In humans, this trace element performs three essential biological roles, as a catalytic, structural and regulatory ion [1-3]. Synthesis of proteins and nucleic acids, RNA transcription, cell apoptosis, and energetic metabolism depend on zinc, which also modulates oxidative stress, inflammation, preservation of cell membrane, and wound healing [4-8].

As an indispensable element for innate and adaptive immunity, endogenous zinc levels can affect count and function of several defense cells, including macrophages, neutrophils, dendritic cells, mast cells, and lymphocytes [9]. Low zinc levels contributes to disruption of cellular function and microcirculation in critically ill patients, manifest either as enhanced inflammation as impaired immunity [10]. In such subjects, accelerated catabolism, systemic inflammatory response and deteriorated nutritional status result in both increased morbidity and mortality [11]. Supplemental nutritional intake with micronutrients, as zinc, selenium and antioxidant vitamins can reduce infections and mortality in these individuals [11].

Elderly usually has a high prevalence of zinc deficiency and a raised susceptibility to infections [12]. Low zinc also occurs in patients feeding enteral nutrition (EN), even when deemed to be nutritionally supplied [13]. This deficiency increases respiratory,

cardiovascular, endocrine, renal, hepatic, immune, infectious, neurological, mental, traumatic, post-operative, gastrointestinal, dermatological, and reproductive disorders [3, 10, 12, 14, 15-25]. Nevertheless, low zinc continues to be a public health problem in all continents, even in developed countries [25].

Since hospitalization is a risk factor for low serum zinc levels, including in critically ill and enteral nutrition inpatients, this study aimed [26]:

1. To measure and compare serum zinc levels in critically ill adult patients fed enteral (EN) or oral nutrition (ON) admitted to a tertiary care general hospital;
2. To correlate these feedings with demographic characteristics, medical conditions, severity score, laboratory tests, and outcome in the evaluated subjects.

Secondarily this research aimed to review nutritional risk of assessed patients at ICU admission.

Methods

This is an observational, analytical, cross-sectional study, carried out in Intensive Care Units (ICU) for adults in a Brazilian private tertiary institution, the São Lucas Hospital (HSL) of Rede D'OR in an association with the Federal University of Sergipe (UFS). Researchers collected data from electronic medical records in 2019. Ethics and Research Committees of UFS and HSL approved this survey by Plataforma Brasil (CAAE: 15805019.0.1001.5546).

We assessed data from ICU patients, categorized into two groups: EN (subjects fed by enteral nutrition) and ON (subjects fed by oral nutrition). A multidisciplinary Nutritional Support Team (NST) followed-up EN and ON groups. The surveyed ICUs were general (20 beds), post-surgical (10 beds) and cardiovascular (10 beds) ones.

Authors excluded medical records of individuals who were fasting for more than 48 hours, fed Parenteral Nutrition, and with malabsorptive diseases.

NRS 2002 (Nutritional Risk Screening 2002), a score frequently applied in Intensive Care, was used as a reference for analysis of nutritional risk [27]. In addition, NST routinely employed indirect calorimetry and, when edema was absence, applied Anthropometry [28]. When oral route failed to provide at least 60% of estimated nutritional needs, NST recommended EN. When subjects could not feed at least 80% of their nutritional needs by only receiving adequate hospital oral diet, NST recommended Oral Supplementation (OS).

Flame atomic absorption spectrophotometry method measured all serum zinc dosages [25, 29]. Normal range: 70 to 120 mcg/dl. Statistical analysis standardized zinc values below 40.0 mcg/dl, i.e. undetectable by the used method, as 40.0 mcg/dl.

Qualitative variables analyzed were sex, principal and secondary diagnoses, ICU type, and mortality. In addition, quantitative variables included zinc, age, leukocytes, hemoglobin, C-reactive protein (CRP), serum iron, and SAPS3 (Simplified Acute Physiology Score 3).

Statistical analysis described qualitative variables by absolute and relative frequency (percentage), and used Chi Square of Pearson and Fisher tests. Mean, median, minimum, maximum, and standard deviation presented quantitative variables. Shapiro-Wilks, Mann-Whitney and Kruskal-Wallis tests evaluated differences in measures of central tendency between groups. Spearman test correlated zinc values with other variables. Significance value of p was ≤ 5%. Software: R Core Team 2020.

Results

The analyzed population had 203 critically ill individuals, of which 137 fed enteral nutrition by tubes or ostomies and 66 fed orally. Most of ICU patients had low serum zinc levels. Further, 29 subjects (24 on EN) had zinc values lower than 40mcg/dl. Figure 1 summarized the distribution of serum zinc levels in both groups.

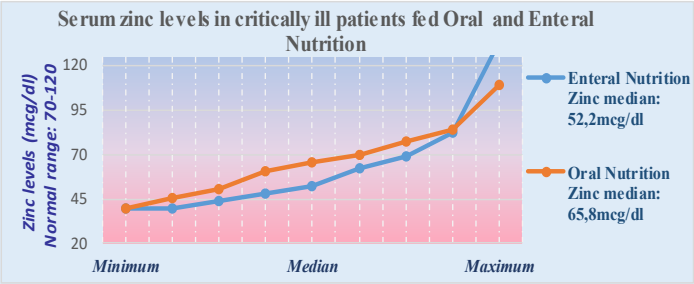

Figure 1: Distribution of Serum Zinc Levels in Critically Ill Patients Fed Oral and Enteral Nutrition.

EN patients had lower serum zinc (59.13 ± 16.26 mcg/dl) and higher mean age (77.48 ± 16.26) than ON group. Table 1 highlighted a comparison of serum zinc, age and biomarkers between EN and ON subjects.

Table 1: Comparison of zinc levels, age and biomarkers between critically ill patients fed Enteral and Oral Nutrition.

	Enteral Nutrition		Oral Nutrition		*p-value*
	n	Mean (SD)	n	Mean (SD)	
Zinc	137	59.13 (16.26)	66	64.75 (16.80)	0.010[MW]
Age	137	77.48 (16.26)	66	75.01 (13.03)	0.012[MW]
C Reactive Protein	98	6.82 (6.76)	64	7.77 (6.88)	0.19[MW]
Iron	91	43.75 (30.24)	64	49.05 (30.65)	0.215[MW]
Hemoglobin	130	10.33 (2.13)	66	10.33 (2.10)	0.887[MW]
White Blood Count (WBC)	130	13.378 (14.813)	66	10.838 (4.675)	0.268[MW]
Simplified Acute Physiology Score 3	90	65.24 (14.51)	48	61.83 (13.81)	0.097[MW]

[MW], Mann-Whitney test; SD, standard deviation. Normal ranges: Zinc= 70-120 mcg/dl; C Reactive Protein< 1.0 mg/dl; Iron= 37-181 mcg/dl; Hemoglobin= 12.0-18.0 g/d; and WBC= 4,000-11,000 cell/mm3.

Table 2 presented a comparison of categorical variables between EN and ON patients. There was a predominance of infection as primary diagnosis and arterial hypertension as secondary diagnosis in both groups. While in ON group there was an expressive prevalence of diabetes mellitus and non-hypertensive heart disease, in EN group there was an important prevalence of dementia. Mortality was higher in EN than in ON group, but without statistical significance.

Table 2: Comparison of demographic and clinical data between critically ill patients fed Enteral and Oral Nutrition.

Clinical data	Enteral Nutrition n (%)	Oral Nutrition n (%)	*p-value*
Sex			
Women	76 (55.5)	34 (51.5)	0.704 [Q]
Main diagnosis			
Cardiovascular disease	13 (9.5)	9 (13.6)	0.279 [Q]
Infection	63 (46.0)	24 (36.4)	
Neurological disease	23 (16.8)	6 (9.1)	
Secondary diagnosis			
Systemic arterial hypertension	75 (56.2)	45 (68.2)	0.103 [Q]
Diabetes Mellitus	41 (29.9)	31 (47.0)	0.020 [Q]
Non-hypertensive heart disease	33 (24.1)	25 (37.9)	0.042 [Q]
Dementia	30 (21.9)	2 (3.0)	<0.001 [F]
Renal failure	51 (37.2)	16 (24.2)	0.057 [Q]
Mechanical ventilation (invasive or non-invasive)	59 (42.3)	35 (53.0)	0.152 [Q]
Type of critical care unit			
General	76 (55.5)	31 (47.0)	0.401 [Q]
Surgical	21 (15.3)	7 (10.6)	
Cardiovascular	27 (19.7)	19 (28.8)	
Unspecified	15 (10.9)	9 (13.6)	
Death	24 (25.5)	11 (18.6)	0.429 [F]

Q Chi-Square of Pearson test; F Fisher test.

Table 3 showed a correlation of quantitative variables with zinc levels. Age presented a negative correlation with zinc dosage in ON group, whereas serum iron presented a positive correlation in EN group. There was a positive correlation of hemoglobin levels with zinc status in both groups tested.

Table 3. Age and biomarkers correlations with serum zinc levels between critically ill patients fed Enteral and Oral Nutrition

	Enteral Nutrition R (p-value)	Oral Nutrition R (p-value)
Age	-0.10 (0.251)	-0.40 (0.001)
Hemoglobin	0.24 (0.007)	0.29 (0.018)
Leukocytes	0.04 (0.620)	-0.08 (0.548)
C Reactive Protein	-0.09 (0.364)	-0.20 (0.114)
Serum iron	0.26 (0.012)	-0.04 (0.776)
SAPS3S	-0.14 (0.198)	0.12 (0.422)

R, Spearman correlation; [S] Simplified Acute Physiology Score 3.

There were no statistically significant results in serum zinc correlation with categorical variables in EN and ON patients. See Table 4 below.

Table 4: Correlation between zinc status and categorical variables in critically ill patients fed Enteral and Oral Nutrition.

	Enteral Nutrition			Oral Nutrition		
	n	Zinc Mean (SD)	p-value	n	Zinc Mean (SD)	p-value
Sex						
Women	76	58,1 (17,5)	0,490 [W]	34	63 (15,5)	0,441 [W]
Main diagnosis						
Cardiovascular disease	13	62 (15,4)	0,620 [K]	9	69,5 (12,5)	0,090 [K]
Infection	63	59,6 (20)		24	59,8 (19)	
Neurological disease	23	62,7 (19,8)		6	67,4 (14,9)	
Secondary diagnosis						
Systemic arterial hypertension	77	60,1 (19,1)	0,529 [W]	45	64,6 (16,7)	0,962 [W]
Diabetes Mellitus	41	57,7 (17,1)	0,581 [W]	31	63,7 (16,6)	0,540 [W]
Non-hypertensive heart disease	33	59,3 (19)	0,958 [W]	25	66,3 (15,3)	0,416 [W]
Dementia	30	61,9 (22,0)	0,509 [W]	2	58,8 (26,6)	0,680 [W]
Renal failure	51	56,3 (16,5)	0,195 [W]	16	62,2 (12,2)	0,653 [W]
Mechanical Ventilation	58	56,8 (17,3)	0,197 [W]	35	61,2 (15,6)	0,066 [W]
ICU type						
Geral	76	59,1 (19,3)	0,145 [K]	31	62,8 (17)	0,189 [K]
Surgical	26	55,3 (16,1)		7	58,4 (20)	
Cardiovascular	20	59,2 (19,7)		19	70,6 (14,5)	
Unspecified	15	65,7 (14)		9	64 (17,6)	
Death	24	57,1 (16,7)	0,616 [W]	11	62,7 (19,4)	0,606 [W]

SD, standard deviation; n, absolute values. [W]Mann-Whitney test; [K]Kruskal-Wallis test. Zinc normal range: 70 to 120 mcg/dl.

The most prevalent nutritional diagnosis at ICU admission was nutritional risk, notably in EN group. Interestingly, in ON group, more than 25% of critically ill patients were overweight or obese, as Figure 1 demonstrated.

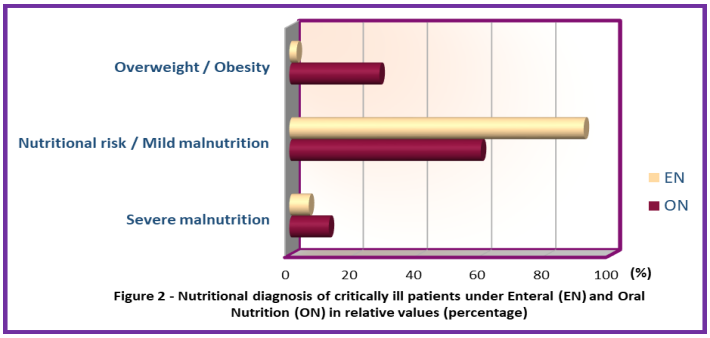

Figure 2 - Nutritional diagnosis of critically ill patients under Enteral (EN) and Oral Nutrition (ON) in relative values (percentage)

Figure 2: Nutritional diagnostics in critically ill patients fed Enteral (EN) and Oral Nutrition (ON), based in NRS 2002 (Nutritional Risk Score 2002).

Enteral diets in EN group provided 100% of RDI (Recommended Daily Intake) of zinc at low flow rate (20 to 30ml/h). In ON group, about 200ml of liquid oral supplements could take 52% to 124% of RDI of zinc. Supplementary Tables 1 and 2 showed details of enteral diets and oral supplements provided in ICU patients.

Discussion

The results of this research showed a high prevalence of zinc deficiency (72%) in assessed patients (see Figure 1), despite only 6.06% EN and 12.28% ON patients presented severe malnutrition, as shown in Figure 2. We also observed that, according to the prescribed nutritional formulations, there was no deficiency of adequate zinc intake for situations without metabolic stress.

These findings are expected, due to high rates of diseases requiring oxidative stress and inflammatory response in this research sample [10, 12, 13, 17]. Newsworthy, an experimental paper has associated low zinc levels with increased ventilator-induced lung injury in ICU [18, 19]. However, currently there is still no consensus on the actual benefit of providing zinc and other trace elements in critically ill patients. Since 2020, Scandinavian researchers have performed a systematic literature review on magnesium, phosphate, and zinc supplements in these individuals [20-30].

In this study, ICU patients had prevalent infectious, neurological and cardiovascular diagnoses, in added to comorbidities such as hypertension, diabetes, dementia and heart disease. Other authors have already correlated low zinc with infectious diseases, especially in septic inpatients with cardiovascular dysfunction [31-33]. Infection changes zinc homeostasis, resulting in redistribution of this trace element into liver to improve acute phase proteins synthesis [34]. Indeed, in response to bacterial and virus diseases, this micronutrient modulates inflammation extent and immune function [31, 35]. Zinc homeostasis in brain tissue affects onset and progression of neurodegenerative disorders, including vascular dementia and Alzheimer's disease [15, 36]. Zinc2+ stabilizes nitric oxide synthase (NOS) structure [1]. NOS is an enzyme, which influences blood glucose, blood pressure, and kidney function [1]. In sepsis, inflammation, ischemia-reperfusion situation, and atherosclerosis, peroxynitrite anion (ONOO-) releases this cation from NOS structure, resulting in superoxide anion accumulate and, thus, increased oxidative stress [1].

Low zinc elderly people characterized EN group, which presented a significant prevalence of dementia and subsequent loss of swallowing ability, demanding an alternative route of nutrition. Despite advances in current dietary formulations, there is still a need for improved intake of specific micronutrients, including zinc, especially in extended EN [37-39]. In senescence, zinc deficiency and corresponding infections can be fatal if not addressed with adequate supplementation [40]. Surprisingly, as contrasted to ON group, there was no significant correlation of low zinc levels with old age in EN group. Probably, in this group, zinc deficiency linked more to diagnoses severity than to age and feeding route.

High SAPS3 score in this investigation (mean>60 in both groups) denoted critical illness severity and presumed a high mortality rate [39]. However, there was no significant difference in correlation of zinc levels with any assessed diagnosis, severity score and outcome. A Brazilian article associated low serum zinc levels with critical illness, but not with its severity, morbidity and mortality [10]. On other hand, a translational research showed that low zinc and selenium concentrations negatively influenced mitochondrial function of human endothelial cells and, in ICU patients, promoted oxidative stress and inflammation damage on energy metabolism [33]. Lee et al have already demonstrated a high mortality in zinc-deficient ICU patients [41].

Our results have supported again a known positive relationship between zinc, iron and hemoglobin levels. However, a competitive absorption process also occurs in concomitant administration of both named microelements [25].

Postoperative ICU evaluated patients presented lower zinc levels than the other ones, but with no statistical significance (see Table 4). Surgical stress results in important metabolic demand for wound healing and injury repair, increases zinc organic consumption and, therefore, reduces its serum levels [1, 7, 8]. As a limitation of this paper, we point out the n, which seems to be insufficient to establish stronger statistical correlations, specifically regarding diagnoses, ICU types, severity criteria and mortality. Furthermore, we believe results could be different for young patients with acute and no previous chronic diseases. More studies are required on this issue.

Also, note that for zinc deficiency, we still lack a clear indicator [42]. In healthy individuals, plasma, serum, urinary, and capillary zinc measurement are reliable biomarkers of body zinc levels [42, 43]. Plasma or serum zinc concentration is the most widely used biomarker to determine zinc status, yet it can be affected by many other factors, including inflammation, fasting or diet, pregnancy, oral contraceptives use, diurnal rhythm, and hypoalbuminemia [42]. We used a recognized and validated technique for serum zinc dosage: flame atomic absorption spectrophotometry method [25, 29, 44]. Although low serum zinc levels could strongly indicate zinc deficiency in this method, normal values do not automatically exclude some degree of disability. Experimental methods, such as a measurement of zinc in lymphocytes, may clarify these cases

[45]. However, these ways have a very high cost and a complex operational management, which preclude their use in medical practice.

Finally, nutritional status affects prognosis of critically ill patients [11]. Early approaches could prevent or treat any malnutrition, in addition low zinc and other micronutrient deficiencies. Thus, we truly believe the follow-up of a multidisciplinary Nutrition Support Team would be advantageous for inpatients, especially in ICUs.

We concluded that zinc deficiency was prevalent in most of critically ill patients evaluated. Subjects fed by enteral nutrition presented lower zinc values them those fed orally. Hemoglobin levels correlated positively with zinc levels in enteral nutrition patients. In those individuals fed by oral route, old age correlated with low zinc levels. Serum iron correlated positively with serum zinc, in both, enteral and oral ICU patients.

The surveyed population presented low prevalence of severe malnutrition at ICU admission.

Zinc supplementation may be required in critically ill patients. Critical Care Team should regarded zinc measurement and supplementation, particularly in subjects feeding by enteral nutrition. Further research are required to improve zinc and other micronutrients supplements in Intensive Care Unit.

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